REMARKS

Claims 1-21 were pending. With this amendment, claims 7 and 8 have been amended. New claims 22-27 have been added. After entry of this amendment, claims 1-27 will be pending and under consideration.

I. AMENDMENTS TO THE SPECIFICATION

The Abstract of the Disclosure has been amended to include the general nature of the compositions and methods disclosed in the instant application.

The specification has been amended on page 7 to make reference to Table 1.

The first table has been amended by inserting "Table 1" before the table.

Tables 1-6 have each been amended by changes in font, font size, and spacings within each of the tables.

Applicants submit that the amendments to the specification do not add new matter and are fully supported by the specification as originally filed. Entry of the amendments to the specification is kindly requested.

II. AMENDMENTS TO THE CLAIMS

Claims 7 and 8 have each been amended by the insertion of the word "the," to correct an obvious grammatical oversight.

New claim 22 recites a chimeric Edg receptor that couples with a Gαq protein comprising an extracellular domain and a transmembrane domain of a first Edg receptor, wherein the first Edg receptor does not couple with a Gαq protein, linked with an intracellular strand of a second Edg receptor that couples with a Gαq protein. Support for new claim 22 is found, for example, on page 12, line 29, to page 13, line 2, page 13, lines 19-25, and page 17, lines 19-26, of the specification.

New claim 23 recites a chimeric Edg receptor comprising, *inter alia*, a chimeric intracellular domain comprising a third intracellular loop and a carboxy terminal strand of a second Edg receptor. Support for this new claim 23 is found in the specification, for example, at page 13, lines 12-18.

New claim 24 recites the receptor of claim 23 wherein the first Edg receptor is selected from the group consisting of Edg1, Edg5, Edg6 and Edg8. New claim 25 recites the chimeric receptor of claim 23 wherein the second Edg receptor is selected from the group consisting of Edg2, Edg3, Edg4 and Edg7. Claims 24 and 25 are each supported by the specification, for example, at page 17, lines 22-24.

New claims 26 and 27 each recite methods of screening for compounds, and are supported respectively by claims 17 and 18 as originally filed, for example.

Applicants submit that the new claims do not add new matter and are fully supported by the specification and claims as originally filed. Entry thereof is respectfully requested.

III. OBJECTION TO THE ABSTRACT OF THE DISCLOSURE

The Patent Office requests a revised Abstract of the Disclosure in the instant application. A revised abstract on a separate sheet has been submitted for entry, as detailed above. Applicants submit that the revised abstract contains the proper content of an Abstract of the Disclosure, and therefore Applicants respectfully request that the objection to the Abstract of the Disclosure be withdrawn.

IV. OBJECTION TO THE TABLES OF THE SPECIFICATION

The Patent Office contends that the numbering of the tables in the specification is confusing because there is no "Table 1," and that Tables 2-6 do not comply with 37 C.F.R. § 1.52(b) with respect to spacing and/or font size. The first table appearing in the specification has been amended by being identified as "Table 1." Tables 1-6 have each been amended to include font size and spacing of lettering compliant with 37 C.F.R. §§ 1.52 and 1.58. Applicants respectfully request that the objections to the tables of the instant application be withdrawn.

V. REJECTION OF CLAIMS 1-21 UNDER 35 U.S.C. § 103(a)

Claims 1-21 stand rejected under 35 U.S.C. § 103(a), allegedly as being obvious over Ancellin & Hla, 1999, *J. Biol. Chem.* 274:18997-19002 in view of any two or more of the following: Conway *et al.*, 2000, *J. Biol. Chem.* 275:20602-20609; Schiöth *et al.*, 1998, *Mol. Pharm.* 54:154-161; Wu *et al.*, 1997, *J. Biol. Chem.* 272:9037-9042; Meng *et al.*, 1996, *Eur. J. Pharm.* 311:285-292; Holtmann *et al.*, 1995, *J. Biol. Chem.* 270:14394-14398; Takagi *et al.*, 1995, *J. Biol. Chem.* 270:10072-10078; Buggy *et al.*, 1995, *J. Biol. Chem.* 270:7474-7478; Kim & Devreotes, 1994, *J. Biol. Chem.* 269:28724-28731; Gether *et al.*, 1993, *J. Biol. Chem.* 268:7893-7898; and Kobilka *et al.*, 1988, *Science* 240:1310-1316. The Patent Office contends since Ancellin & Hla teach that the structurally related sphingosine 1-phosphate ("S1P") G protein-coupled receptors ("GPCRs") Edg-1, Edg-3 and Edg-5 have pharmacologically distinct responsiveness to S1P, claims 1-21 of the instant

application are *prima facie* obvious in view of the other cited references teaching chimeric GPCRs, none of which teach a chimeric Edg receptor.

Applicants respectfully traverse the rejection of claims 1-21 under 35 U.S.C. § 103(a). Applicants respectfully submit that, with regard to claims 1-21, *prima facie* obviousness is not shown in view of Ancellin & Hla on the mere fact that a variety of chimeric GPCRs may have been exemplified by the other cited references. Claims 1-21 are not methods for analyzing the structure or function of GPCRs generally, but are claims directed to particular Edg chimeras (*i.e.*, independent claim 1 and claims 2-13 depending from claim 1) having particular structures and useful properties, or else claims directed to nucleic acids or cells comprising these particular Edg chimeras (*i.e.*, claims 14-16), or methods of screening compounds using these particular Edg chimeras (*i.e.*, claims 17-21). Nothing in the combination of cited references teaches or suggests the Edg chimeras recited in any of claims 1-21.

The Patent Office bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); MPEP § 2142. The legal standard of *prima facie* obviousness requires that three criteria be met. First, the prior art either alone or combination must teach or suggest each and every claim limitation. *In re Wilson*, 165 U.S.P.Q. 494, 496 (CCPA 1970). Second, there must a suggestion or motivation in the cited references or in the art to modify or combine the cited references. *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1456 (Fed. Cir. 1998). The showing of a motivation to combine the references that create the case of obviousness is required to prevent the use of hindsight based on the invention to defeat patentability of the invention. *Id.* at 1457-58. "In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* The third criteria is that the cited references must provide a reasonable expectation of successfully achieving the claimed invention. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

Applicants respectfully submit that none of Conway *et al.*, Schiöth *et al.*, Wu *et al.*, Meng *et al.*, Holtmann *et al.*, Takagi *et al.*, Buggy *et al.*, Kim & Devreotes, Gether *et al.*, and Kobilka *et al.*, either alone or in any combination suggest or motivate one of ordinary skill in the art to produce a chimeric Edg receptor comprising the extracellular and transmembrane domains of a first Edg receptor and a chimeric intracellular domain comprising an intracellular strand of a second Edg receptor, wherein the chimeric intracellular domain is

operably linked to the transmembrane domain, as recited in claim 1 of the instant application. Moreover, none of the cited references, or any combination of the cited references, indicates that producing the chimeric Edg receptor of claim 1 or any of claims 2-21 which depend directly or indirectly from claim 1, would have the particular useful features as described in the instant application.

The Patent Office acknowledges that Ancellin & Hla do not teach construction of chimeric Edg receptors. Moreover, while Acellin & Hla teach coupling of Edg3 receptor to a Gαq protein, these authors do not teach or suggest substitution of any portion of an Edg3 receptor, *e.g.*, an intracellular strand, as recited in claim 1.

The Patent Office cites Conway *et al.*, Schiöth *et al.*, Wu *et al.*, Meng *et al.*, Holtmann *et al.*, Takagi *et al.*, Buggy *et al.*, Kim & Devreotes, Gether *et al.*, and Kobilka *et al.*, for the reason that each publication describes the construction of a number of chimeric GPCRs. Yet, not one of these GPCRs is an Edg receptor. Not one of the cited papers suggests making similar chimeras in an Edg receptor. Moreover, almost all of the 112 or so chimeras comprise structural substitutions to an GPCR that have no relation to, and in fact teach away from, the specific chimeric receptor recited in claim 1. For instance, the large majority of the chimeric GPCRs in references cited by the Patent Office comprise transmembrane domain substitutions of a GPCR, in contrast to the specific intracellular domain chimeras of claim 1. A number of chimeric GPCRs in the references include substitution of extracellular domain strands, which stands in contrast to the specific intracellular domain chimeras of claim 1. Applicants respectfully submit that the combination of cited references fails to teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first Edg receptor are linked to a chimeric intracellular domain comprising an intracellular strand of a second Edg receptor.

To illustrate, Conway *et al.*, in Figure 3, teach fourteen chimeras of human melatonin mt_1 receptor and melatonin-related receptor used to assess melatonin-binding and ability to increase cAMP in cells. The chimeras of Conway *et al.* are pieced together differently than any chimeric Edg receptor of claim 1. For example, each chimeric GPCR in Conway *et al.* has at least one, if not more, transmembrane helices plus linked extracellular or intracellular strands from one GPCR substituted into another GPCR. Applicants submit that Conway *et al.* do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR are linked to a chimeric intracellular domain comprising an intracellular strand of a second GPRC.

Schiöth *et al.*, in Figure 2, teach eight chimeras of melanocortin MC1 and MC3 receptors assessed for ligand binding and ability to increase cAMP in cells. Like Conway *et al.*, Schiöth *et al.* teach away from constructing a chimera that would be analogous to anything claimed by Applicants. In Schiöth *et al.*, chimeric melanocortin receptors are produced by substituting at least one extracellular strand, one transmembrane helix and one intracellular domain of one melanocortin receptor subtype into the other subtype. In most chimeras more than just one transmembrane helix are substituted. Schiöth *et al.* do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR are linked to a chimeric intracellular domain comprising an intracellular strand of a second GPRC.

Wu *et al.*, in Figure 1, teach six human cholecystokinin ("CCK") receptor chimeras of CCK-AR and CCK-BR subtypes constructed to determine the structural basis of CCK-AR functionally coupling to G_s, a G protein that stimulates adenylyl cyclase leading to cAMP production. To Applicant's knowledge, no Edg receptor has been reported to be linked to G_s, rendering the chimeras constructed by Wu *et al.* of little import to the instant application. Even so, five of the CCK chimeras in Wu *et al.* are constructed by substituting either the amino terminal extracellular strand and/or strands encompassing transmembrane helices from one CCK receptor subtype into another. Such substitutions are unlike any chimeric receptor structure claimed by Applicants. One chimeric CCK receptor, termed "BA_{ICL-1}," has five residues in a the first intracellular loop of the CCK-BR receptor replaced with the corresponding residues from the CCK-AR, but this chimera had a reduced calcium response in comparison to either of the wildtype CCK receptors (*see* Wu *et al.*, Table II), which teaches away from Applicants' Edg chimeras. Thus, Applicants submit that Wu *et al.* do not teach or suggest to those of ordinary skill in the art that they should make a chimeric receptor wherein the extracellular domain and transmembrane domain of a first Edg receptor are linked to a chimeric intracellular domain comprising an intracellular strand of a second Edg receptor.

Meng *et al.*, in Tables 1 to 3, teach twenty-three chimeras of the δ-, κ-, and μ-opioid receptors that are assessed for opioid ligand selectivity. One look at the seven segments of the opioid receptors that Meng *et al.* swap between different receptors and it is clear that these segments each consist of either an extracellular strand or else one or more transmembranes helices. The segments Meng *et al.* substitute between receptors do not suggest the substitutions in Applicant's claimed chimeric receptors. Meng *et al.* do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain

of a first GPCR are linked to a chimeric intracellular domain comprising an intracellular strand of a second GPCR.

Holtmann *et al.*, in Figures 1 and 5, teach six chimeras of a secretin receptor and a vasoactive intestinal polypeptide (VIP) receptor assessed for cAMP response and ligand binding. The chimeric GPCRs in Holtmann *et al.* are composed of chimeric segments that do not correspond in structure to the chimeric receptors claimed by Applicants. The chimeras in Holtmann *et al.* are composed of combinations in which the amino terminal extracellular strand or first extracellular loop, or both, have been transferred from one receptor to the other. Applicants submit that Holtmann *et al.* do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR are linked to a chimeric intracellular domain comprising an intracellular strand of a second GPCR.

Takagi *et al.* teach eight chimeras of the human endothelin type A ("ET_A") and type B ("ET_B") receptors. In contrast to the structure of Applicant's claimed chimeras, seven of the Takagi *et al.* chimeras are built using regions including at least one, usually two or more, transmembrane helices. One chimeric receptor is composed of the ET_A receptor with a carboxy terminal strand from ET_B, but this particular chimera is not preferred in that this region was not involved in the selective activation of G_s or G_i. Applicants submit that Takagi *et al.* do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first Edg receptor are linked to a chimeric intracellular domain comprising an intracellular strand of a second Edg receptor.

Buggy *et al.*, in Figure 2, teach ten chimeras of the human glucagon receptor ("hGR") and human islet GLP-I receptor ("GLP-IR") each assessed for glucagon binding. Glucagon binding is not a feature associated with Applicants' chimeric Edg receptors, indicating that Buggy *et al.* is hardly relevant to Applicants' claims. Nonetheless, nine of the Buggy *et al.* chimeras involved chimeric GPCR segments that are structurally distinct from Applicants' claimed chimeric receptors. For example, chimera "CH-10" of Buggy *et al.* consists of hGR with a third extracellular loop taken from GLP-IR. One chimera, termed "CH-5," of Buggy *et al.* is a hGR with a substituted second intracellular loop from GLP-IR, and this receptor was found to bind glucagon with an affinity similar to hGR indicating that this loop is probably not involved in glucagon binding. Indeed, Buggy *et al.* teach away from the structural substitutions of Applicants' chimeric Edg receptors by stating that all three intracellular loops and entire carboxy terminal tail are not involved in selective binding of glucagon (page 7476, left col.). Applicants respectfully do not see how Buggy *et al.* suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first

Edg receptor are linked to a chimeric intracellular domain comprising an intracellular strand of a second Edg receptor.

Kim & Devreotes, in Table 1, Figures 2, 5 and 6, teach twenty-two cAMP chemoattractant receptor chimeras composed of the cAR1 and cAR2 subtypes that were analyzed for cAMP binding. Portions of these GPCRs that were substituted between the cAR1 and cAR2 receptors include a portion of the carboxy terminal strand, the entire carboxy terminal strand, or the carboxy terminal strand plus additional portions of a receptor. Focusing on a region between the fourth and fifth transmembrane helices, described by Kim & Devreotes as being most significant for high affinity cAMP binding, additional chimeras were produced with just this portion being substituted between the two receptor subtypes. This structural region does not suggest the chimeric intracellular domain of Applicants' Edg receptors, for example, as in claim 1. Moreover, to Applicants' knowledge, Edg receptors do not even bind cAMP, rendering the work of Kim & Devreotes of little consequence to Applicants' claims. Applicants submit that Kim & Devreotes do not suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR are linked to a chimeric intracellular domain comprising an intracellular strand of a second GPCR.

Gether *et al.*, in Table 1 and Figures 1 & 2, teach five chimeric NK_1 (substance P) and NK_3 (neurokinin B) receptors that are assessed for peptide agonist selectivity. In clear contrast to chimeric intracellular domain that is recited in claim 1 of the instant application, each of swapped segments in Gether *et al.* includes an extracellular strand and transmembrane region. The structural features of the chimeras in Gether *et al.* do not correspond to the structural features of Edg receptors claimed by Applicants. Gether *et al.* do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR are linked to a chimeric intracellular domain comprising an intracellular strand of a second GPCR.

Kobilka *et al.*, in Figures 1-3 and 5-8, teach ten chimeric adrenergic receptors in which portions of the α_2 and β_2 adrenergic receptors have been substituted. At a minimum, each portion consists of at least one transmembrane helix. Thus, the chimeras of Kobilka *et al.* comprise substituted structures altogether different from the chimeric intracellular domain described by Applicants. Kobilka *et al.* do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR are linked to a chimeric intracellular domain comprising an intracellular strand of a second GPRC.

Despite the large number of references cited by the Patent Office, Applicants respectfully submit that the standard of *prima facie* obviousness has not been met by the Patent Office. It may be that, to use the Patent Office's own words, the references suggest a variety of chimeric receptors "for the purpose of identifying those structural domains in each of those two related receptors that are responsible for the specific pharmacological properties of that receptor" (pages 5-6 of the Office Action). But, as explained above, the vast majority of structural portions that are substituted in the chimeric GPCRs of the cited references are not, and do not suggest, the structural portions that Applicants have substituted in a receptor of claims 1-22. This conglomeration of chimeric receptors pointed to by the Patent Office simply provides no teaching, no suggestion, indeed no motivation to one of skill in the art faced with the same problems as the Applicants, to select the elements from the cited references for combination in the manner claimed by Applicants in any of claims 1-21. Accordingly, Applicants respectfully request that the Patent Office withdraw the rejection of claims 1-21 under 35 U.S.C. § 103(a).

Applicants submit that new claims 22-27 meet the requirements for patentability under 35 U.S.C. § 103(a). Not one of the cited references of Ancellin & Hla, Conway *et al.*, Schiöth *et al.*, Wu *et al.*, Meng *et al.*, Holtmann *et al.*, Takagi *et al.*, Buggy *et al.*, Kim & Devreotes, Gether *et al.*, and Kobilka *et al.*, alone or in any combination, teach or suggest a chimeric Edg that couples with a Gαq protein comprising an extracellular domain and a transmembrane domain of a first Edg receptor, wherein the first Edg receptor does not couple with a Gαq protein, linked with an chimeric intracellular domain comprising an intracellular strand of a second Edg receptor, wherein the intracellular strand of the second Edg receptor couples with a Gαq protein, as recited in new claim 22. Nor do any of the cited references, alone or in combination, teach or suggest a chimeric Edg receptor comprising the extracellular domain and transmembrane domain of a first Edg receptor and a chimeric intracellular domain comprising a third intracellular loop and a carboxy terminal strand of a second Edg receptor, wherein the chimeric intracellular domain is operably linked to the transmembrane domain, as recited in new claim 23. Applicants further submit that none of the cited references, alone or in combination, teach or suggest the chimeric receptor of claims 24 or 25, or the methods of screening for compounds recited in claims 26 or 27.

CONCLUSION

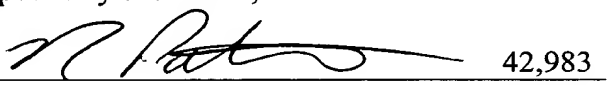
In view of the above remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 849-7607.

No fees, other than those for an extension of time, are believed due with this response. However, the Commissioner is authorized to charge any fees under 37 C.F.R. § 1.17, any underpayment of fees, or credit any overpayment to Pennie & Edmonds$_{LLP}$ U.S. Deposit Account No. 16-1150 (order no. 10602-013-999) that may be required by this Amendment and Response.

Respectfully submitted,

Date: July 10, 2003



42,983

Rahul Pathak (Reg. No.)
For: Nikolaos C. George (Reg. No. 39,201)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090